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Systematic identification of the druggable interactions between human protein kinases and naturally occurring compounds in endometriosis.

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Abstract

Diverse kinase signaling pathways have been involved in the pathogenesis of endometriosis (EM), which can be modulated either by directly targeting the hub kinases or by indirectly regulating marginal members in the pathways. Here, a systematic kinase-inhibitor interaction profile was created for 8 naturally occurring compounds against 20 human protein kinases. The compounds are all non-sterid that have been reported as pharmacologically active molecular entities potential for EM therapeutics, while the kinases were curated via gene ontology terms enriched from the gene co-citation network with EM. The resulting profile was analyzed at structural, energetic and dynamic levels to identify druggable kinase-compound interactions. The compounds Gossypol, Curcumin and EGCG showed a similar interaction profile across these kinases; they can bind tightly to the top-listed kinases in gene ontology, while the compounds Marrubiin, Apigenin and DIM were predicted to exhibit generally weak affinity for the 20 curated kinases. The JNK kinase, a MAPK family member, was identified as a putative candidate of druggable target for EM therapeutics; the inhibitory activity of eight naturally occurring compounds as well as a sophisticated kinase inhibitor SP600125 against the JNK was tested using enzymatic activity analysis. As might be expected, the Gossypol and EGCG were determined to have high inhibitory activity at namomolar level (IC_{50}=55 and 94nM, respectively), which are comparable with or better than the positive control SP600125 (IC_{50}=76nM), while other tested compounds exhibited weak inhibition (IC_{50}>100nM) or bad potency (IC_{50}=n.d.) against the kinase.